Drosophila development: **A prepattern for sensory organs**

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The sensory bristles of *Drosophila* arise in stereotyped positions from small clusters of cells that express *achaete–scute* genes. A set of genes has now been identified that regulate *achaete–scute* expression and form a prepattern for sensory bristle development.

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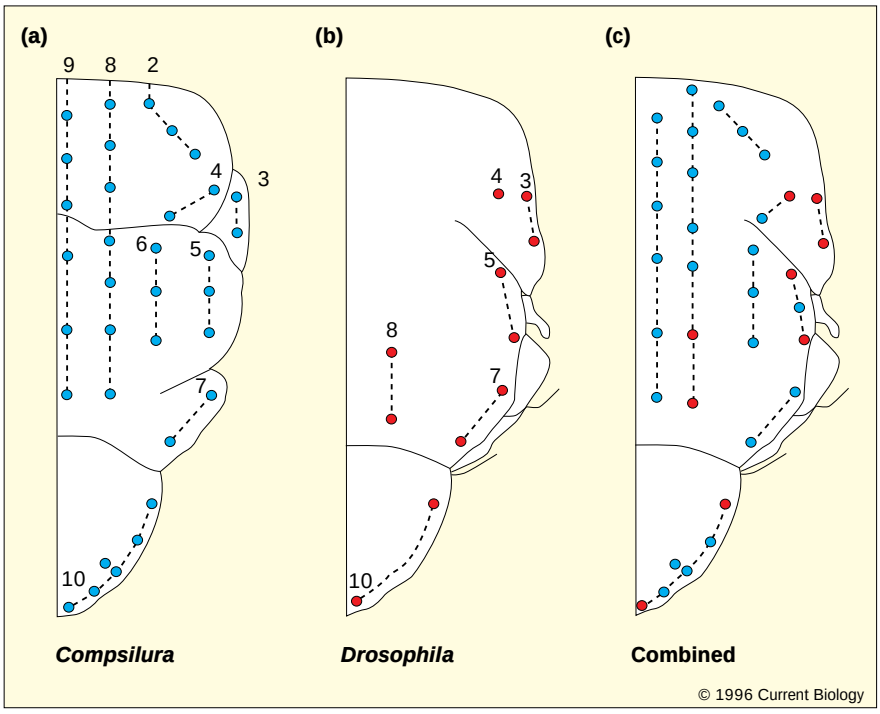
The bristles and wing veins of *Drosophila* are ideal for studying the generation of spatial patterns. Sensory bristles occupy stereotyped positions of importance to the animal, as the neuronal specificity of bristles depends upon the site in the epithelium at which they are born. The thoracic bristle pattern has been conserved throughout the 2000 or more species of this genus and is well over 50 million years old; there has thus been a long period for stabilization by natural selection. Primitive insects were covered with uniformly spaced bristles. The Dipteran thorax is characterized by rows of spaced, large bristles, known as macrochaetes (Fig. 1a; the rows of small bristles, or microchaetes, are not shown). During the evolution of Diptera, however, many of the large bristles have been lost from the pattern, so that in *Drosophila* some rows have been lost entirely and only vestiges of most of the other rows remain (Fig. 1b,c).

Each bristle develops from a single cell, the sensory organ precursor, which divides to produce the four cells that construct the bristle organ. The proneural genes *achaete* (*ac*) and *scute* (*sc*), which encode basic helix–loop–helix DNA binding proteins, are paramount for bristle development: they confer the ability to make sensory organ precursors [1,2]. In the *Drosophila* thorax, the *ac–sc* genes have very dynamic expression patterns at the sites of the future bristles [1,2]. The microchaete rows arise from stripes of cells expressing *ac–sc* genes, which subsequently resolve into single-spaced sensory organ precursors that continue to express *ac–sc* until they divide and differentiate. Macrochaetes arise from small groups of *ac–sc*-expressing cells known as proneural clusters, which resolve into one or a few *ac–sc*-expressing sensory organ precursors [1,2]. Within the *ac–sc*-expressing territories, cell–cell interactions mediated by Notch and Delta are responsible for singling out the sensory organ precursors and for downregulating

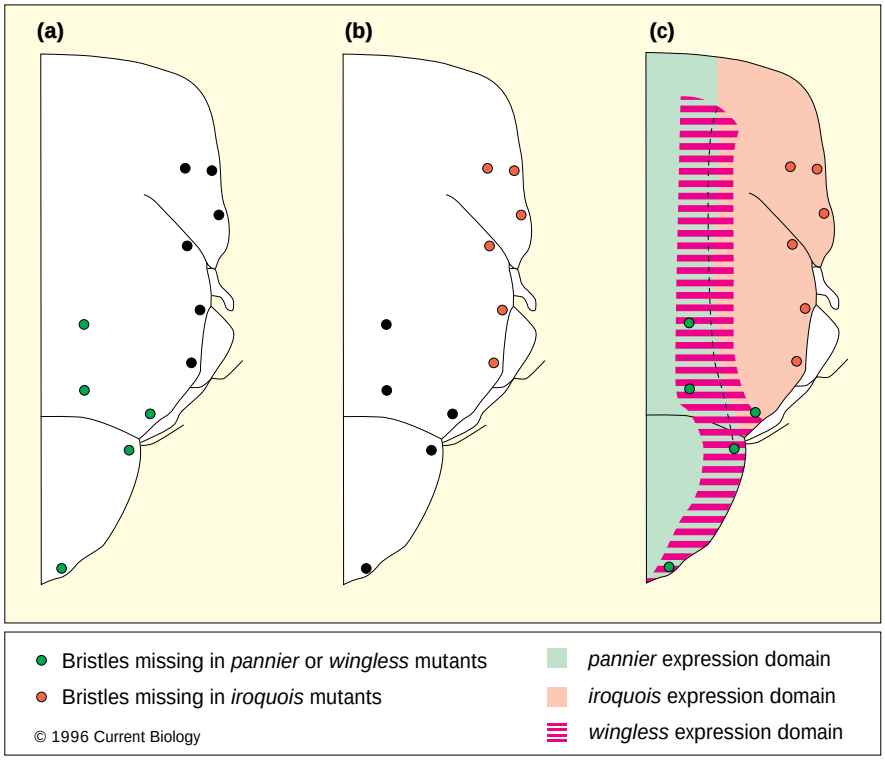
Figure 1



Thoracic bristle patterns in Diptera. The arrangement of macrochaetes has been of immense value in the classification of Diptera. The full Dipteran pattern is illustrated in (**a**) for the calypterate tachynid *Compsilura cocinnata*. The notum is more or less covered with rows of evenly spaced macrochaetes. The numbers correspond to defined, named bristle rows. The *Drosophila* pattern (**b**) shows a reduction in bristle numbers from the full pattern, there being a tendency throughout evolution to lose the more anteriorly placed bristles. The two patterns are superimposed for comparison in (**c**).

Figure 2

Effects of mutations on the *Drosophila* bristle pattern. Mutations of *pannier* and *wingless* affect five macrochaetes situated on the medial half of the thorax (**a**), whereas mutations of *iroquois* affect the complementary set of bristles on the lateral half (**b**). The superimposed expression domains of the three genes is shown in (**c**): *pannier* is expressed in a broad medial band extending the length of the notum, and *iroquois* is expressed in a complementary band on the lateral half; *wingless* is expressed in a medio-lateral stripe overlapping the *pannier* and *iroquois* domains.



ac–sc expression in neighbouring cells; this mechanism ensures that no two sensory organ precursors develop adjacent to one another.

The positions of the proneural clusters prefigure the sites at which the macrochaetes develop, so the precise control of *ac–sc* expression to some extent determines bristle positions. There seem, however, to be redundant mechanisms for constructing the pattern: ubiquitous expression of *sc* in absence of the endogenous *ac–sc* genes allows the development of bristles that arise at the correct sites [3]. There must thus be factors distributed asymmetrically in the epithelium that control not only transcription of the *ac–sc* genes but also the activity of their products. This has led to the notion that there are 'prepattern' genes for bristle development, of the kind first postulated by Stern [4]. These genes would act between those controlling the subdivision of imaginal discs into large domains or compartments, and the finer control of *ac–sc* expression. One factor that is asymmetrically expressed in the thoracic epithelium is the product of the *extramacrochaetae* (*emc*) gene, a helix–loop–helix protein devoid of a basic domain that is thought to sequester Ac–Sc proteins, preventing them from binding to DNA [1,2]. The *emc* gene furthermore displays an expression pattern more or less complementary to that of *ac–sc* — high levels are found at sites of low *ac–sc* expression [1,2]. The distribution of Emc may thus account for the fact that bristles arise at normal positions after ubiquitous *sc* expression.

The activation of *ac–sc* at specific sites must of course be dependent upon transcriptional regulators, and so far two loci have been identified that encode transcription factors which influence the pattern of macrochaetes: *pannier* (*pnr*) and *iroquois* (*iro*). Interestingly, these genes affect complementary subsets of bristles and are expressed in complementary patterns in the thoracic epithelium (Fig. 2). The *pnr* gene is expressed in a broad band on the medial half of the thorax and affects bristles in this domain [5,6], whereas *iro* is expressed in a broad band on the lateral half of the thorax and affects bristles within this area [7,8]. The *pnr* gene product is a zinc-finger protein of the GATA family [5]. Mutations of *pnr* cause either a loss or a gain of bristles, and activity of this gene seems to result in either activation or repression of *ac–sc*, dependent on the presence of additional cofactors ([6]; P. Heitzler, P. Ramain, M. Haenlin, Y. Cubadda and F. Blondeau, personal communication). It is not yet known whether Pnr acts directly on the transcription of *ac–sc*. Two genes reside at the *iro* locus, *caupolican* and *araucan*; these display similar expression patterns and both encode homeobox-containing proteins [8]. Mutation of either of the *iro* genes causes a loss of the bristles in the *iro* expression domain, and the products of these genes have now been shown to regulate *ac–sc* expression directly [8].

The *cis*-regulatory elements of the *ac–sc* complex are widely dispersed. Many *ac–sc* mutants display losses of subsets of macrochaetes and are associated with breakpoints in the complex, some of which are 50 kilobases or more downstream of the coding sequences. Small, discrete regulatory regions capable of driving *lacZ* expression at specific positions in the thorax and wing have recently been defined by Juan Modolell and colleagues [9] and by others (B. Marie and M. Bourouis, personal communication). These enhancers control the coordinate expression of *ac–sc* [9]. The complex pattern is thus generated piecemeal through the action of separable elements. One of the enhancers drives *ac–sc* expression along the anterior wing margin and the third vein (L3/TSM), where it is required for the generation of particular sensilla [9]. This element was defined in more detail and sequence analysis revealed the presence of a TAAT tetranucleotide; TAAT is a common motif in the consensus binding sites of many homeodomain proteins.

As well as being expressed in the thorax, the *iro* genes are expressed in parts of the wing where they are important for the pattern of both sensilla and veins. Genetic analysis has revealed interactions between *iro* and vein-patterning genes [8]. Mutations that cause a reduction in *iro* expression result in a corresponding loss of *ac–sc* products along the anterior wing margin and the third vein. Furthermore, the Araucan protein was shown to bind to the TAAT motif in the L3/TSM enhancer, and is thus likely to activate *ac–sc* directly through this enhancer [8]. This is thus the first demonstration of a direct activator of *ac–sc* transcription.

The *iro* and *pnr* genes, which are expressed in broad domains in the imaginal discs and act upstream of *ac–sc*, may therefore correspond to the 'prepattern' genes postulated by Stern [4]. They are expected to act downstream of genes that provide positional information. Positional information is given by the activity of genes encoding signalling proteins, such as *hedgehog*, *wingless* (*wg*) and *decapentaplegic*, which are themselves dependent upon the prior subdivision of imaginal discs into compartments by the selector genes *engrailed* and *apterous*.

It is of interest that *iro* and *pnr* are expressed in longitudinal stripes along the thorax which are aligned with the bristle rows (Fig. 2). In fact, *wg* is also expressed in a mediolateral stripe that overlaps the domains of both *pnr* and *iro* ([10]; Fig. 2); *wg* is required for development of the same subset of bristles as *pnr*. The rows of thoracic bristles seen in many Diptera (Fig. 1a) may therefore be the result of an underlying stripe-like patterning information. Indeed, mutants of *Drosophila* in which the levels of *emc* activity are reduced display more primitive patterns of rows of macrochaetes [11], possibly reflecting cryptic expression of *ac–sc* in stripes. Further studies on this class of gene should lead to a better understanding of the generation of the spatial patterns of bristles.

References

1. Campuzano S, Modolell J: Patterning of the ***Drosophila*** nervous system: the achaete–scute gene complex. *Trends Genet* 1992, 8:202–208.
2. Ghysen A, Dambly-Chaudière C, Jan LY, Jan Y-N: Cell interactions and gene interactions in peripheral neurogenesis. *Genes Dev* 1993, 7:723–733.
3. Rodriguez I, Hernandez R, Modolell J, Ruiz-Gomez M: Competence to develop sensory organs is temporally and spatially regulated in ***Drosophila*** epidermal primordia. *EMBO J* 1990, 9:3583–3592.
4. Stern C: Two or three bristles. *Am Sci* 1954, 42:213–247.
5. Ramain P, Heitzler P, Haenlin M, Simpson P: ***pannier***, a negative regulator of ***achaete*** and ***scute*** in ***Drosophila***, encodes a zinc finger protein with homology to the vertebrate transcription factor GATA-1. *Development* 1993, 119:1277–1291.
6. Heitzler P, Haenlin M, Ramain P, Calleja M, Simpson P: A genetic analysis of ***pannier***, a gene necessary for viability of dorsal tissues and bristle positioning in ***Drosophila***. *Genetics* 1996, in press.
7. Dambly-Chaudière C, Leyns L: The determination of sense organs in ***Drosophila***: a search for interacting genes. *Int J Dev Biol* 1992, 36:85–91.
8. Gomez-Skarmeta J-L, Diez del Corral R, de la Calle-Mustienes E, Ferres-Marco D, Modolell J: ***araucan*** and ***caupolican***, two members of the novel ***iroquois*** complex, encode homeoproteins that control proneural and vein-forming genes. *Cell* 1996, 85:95–105.
9. Gomez-Skarmeta J-L, Rodriguez I, Martinez C, Culi J, Ferres-Marco D, Beamonte D, Modolell J: ***Cis***-regulation of ***achaete*** and ***scute***: shared enhancer-like elements drive their coexpression in proneural clusters of the imaginal discs. *Genes Dev* 1995, 9:1869–1882.
10. Phillips RG, Whittle R: ***wingless*** expression mediates determination of peripheral nervous system elements in late stages of ***Drosophila*** wing disc development. *Development* 1993, 118:427–438.
11. Moscoso del Prado J, Garcia-Bellido A: Cell interactions in the generation of chaetae pattern in ***Drosophila***. *Roux's Arch Dev Biol* 1984, 193:246–251.